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Research Article

Clinical Outcome of Using Remdesivir in Bangladeshi Hospitalized Patients with Severe Coronavirus Disease (COVID-19)

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Abstract

Background: Remdesivir is a broad-spectrum antiviral agent that is the first and only available therapeutic drug that has been approved by several regulatory bodies for clinical use in the management of patients with severe COVID-19. Aim of this study was to evaluate the clinical outcome and safety of using Remdesivir in Bangladeshi hospitalized patients with severe COVID-19.

Methods: We conducted a randomized, controlled, open level trial of intravenous Remdesivir in adult patients who are hospitalized with Covid-19. Patients were randomly assigned to receive standard of care therapy together with Remdesivir 200 mg on day 1 followed by Remdesivir 100 mg for next 4 days or standard of care therapy only. The primary clinical endpoint was duration of hospitalization, defined by either discharge from the hospital or hospitalization for infection control purposes only.

Results: A total of 60 patients were enrolled in the study after screening. Mean age of all the patients was 53.2 ± 12.7 and 83.3% were male. Results indicated that patients in the Remdesivir group had significantly shorter mean duration of hospitalization than control group (mean ± SD 7.3 ± 2.4, as compared to 10.8 ± 6.1; p-value: 0.013). In cox proportional hazard regression comparing time to clinical improvement (TTCI), we found statistically significant difference on day 11 (HR - 1.88; 95% CI - 1.03 - 3.36; p-value - 0.038) and day 14 (HR - 2.15; 95% CI - 1.22 - 3.81; p-value - 0.008) between two groups. There was no mortality or serious adverse events among all the patients in both groups.

Conclusion: Remdesivir was proved to be beneficial to shorten the duration of hospitalization and time to clinical improvement in adult patients requiring supplemental oxygen therapy. A randomized placebo controlled clinical trial with larger sample size appears to be warranted to validate these important findings.

Keywords: COVID-19; Remdesivir; SARS-CoV-2

Introduction

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is an unprecedented global health crisis of the 21st century [1]. It was first identified in Wuhan, China, December 2019 [2]. Being a highly contagious virus, SARS-CoV-2 has spread throughout the world and put enormous challenge to the global socioeconomic and healthcare sectors [3]. The World Health Organization (WHO) announced COVID-19 as a global health emergency on 30th January 2020 [4] and a global pandemic on 11 March, 2020 [5]. The first case of Bangladesh was reported on March 8, 2020 and first fatality on April 1, 2020 [6]. Between 8 March 2020 and 20 June 2021, according to the DGHS Press Release there were 851, 668 COVID-19 cases confirmed by RT-PCR, GeneXpert, and Rapid Antigen tests and 13,548 related deaths (CFR 1.59%). Bangladesh is among the top 31 countries and accounts for 0.48% of the COVID-19 cases of the world [6].

Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from asymptomatic infection or mild respiratory symptoms to life-threatening pneumonia and death. There is no definitive curative treatment for COVID-19 till now and high mortality rate is seen among vulnerable populations [7]. Health authorities are focusing on the repurposing of available drugs to develop timely and cost-effective remedial strategies specially for the hospitalized critical patients.

Remdesivir is a broad-spectrum antiviral agent that has previously demonstrated antiviral activity against the Ebola virus *in vitro* and in animal models but failed to demonstrate efficacy in randomized clinical trials [8,9]. Later, Remdesivir was shown to exhibit antiviral activity against SARS-CoV-2 *in vitro* studies, and it was proposed as an investigational drug early during the pandemic [10]. It has been considered as a 'molecule of hope' for the treatment of COVID-19 and was the only authorized drug for use under an Emergency Use Authorization as it showed promising results in several studies. and On the 22nd October 2020, Remdesivir was authorized as the first antiviral drug by the United States Food and Drug Administration (FDA) for the treatment of hospitalized COVID-19 patients [11,12]. Remdesivir has shown protective efficacy of other human coronaviruses including severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [13]. Efficacy and safety of Remdesivir has also been demonstrated in animal models in COVID-19 and data from human trials [14-16]. The ACTT-1 (Adaptive COVID-19 Treatment Trial) trial showed that patients with advanced COVID-19 and lung involvement who received 10-days of Remdesivir recovered faster than similar patients who received placebo. Also, Remdesivir showed prevention of more severe disease progression as well as a lower incidence of new oxygen use, use of high flow oxygen, or mechanical ventilation or ECMO [17]. Also there was less disease progression or mortality in comparison with placebo group in non-mechanically ventilated patients as showed in the post hoc analysis [18].

The treatment guideline of Bangladesh for COVID-19 included several drugs for severely ill patients who required hospitalizations [19]. Physicians of Bangladesh have been prescribing numerous medications, including Remdesivir and Ivermectin for the treatment of COVID-19 [19]. But, there is no study has been done so far in Bangladeshi patients to explore the efficacy and safety of Remdesivir.

Aim of the Study

Aim of this randomized, controlled, open label trial was to evaluate the clinical outcome of using Remdesivir in Bangladeshi hospitalized patients with severe COVID-19.

Methods

This was a randomized, controlled, open level trial conducted in Combined Military Hospital, Dhaka, Bangladesh. Ethical approval was obtained from the institutional review boards of the hospital. Written informed consent was obtained from all patients, or their legal representative if they were unable to provide consent. The trial was done in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization-Good Clinical Practice guidelines. The protocol is available online.

Eligible patients were men and non-pregnant women with COVID-19 who were aged at least 18 years and hospitalized with diagnosed COVID-19 confirmed by RT-PCR test ≤ 7 days before randomization with respiratory distress (≥ 30 breaths/min) or finger oxygen saturation ≤ 93% at rest or arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg. Exclusion criteria included Severe liver disease (Alanine Transaminase (ALT) or Aspartate Transaminase (AST) > 5 times the upper limit of normal); Severe renal failure (Estimated glomerular filtration rate (eGFR) < 30 ml/min and patients receiving hemodialysis or hemofiltration); mechanically ventilated (including V-V ECMO) ≥ 5 days,

or any duration of V-A ECMO; Known hypersensitivity to the Remdesivir, the metabolites, or formulation excipient; Pregnancy or breast feeding; anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours and if physician made a decision that trial involvement is not in patients' best interest, or any condition that did not allow the protocol to be followed safely.

Eligible patients were randomly assigned to 2 treatment arms at a ratio of 1:1, and participants in 2 groups had different treatment based on the assigned treatment arm. Sixty patients were randomized between September 2020 to March 2021. The permuted block (6 patients per block) randomization sequence, including stratification, was prepared by a statistician not involved in the trial using SAS software. After randomization, Eligible patients were allocated a unique randomization number which cannot under any circumstance be reallocated to any other participants. Envelopes were prepared for emergency unmasking.

All patients received the standard medical care for COVID-19 at the hospital. Patients were assessed once daily by trained nurses using diary cards and vital signs were recorded every 24 hours till discharge or as per the discretion of the attending physicians. In one arm, participants received continued standard of care therapy together with Remdesivir 200 mg on day 1 followed by Remdesivir 100 mg for next 4 days. In other arm, participants received continued standard of care therapy only. Patients safety assessment e. g. blood parameters (CBC, SGPT, RBS, Creatinine, Creatinine Clearance) was done on screening, day 5 and day 14 or on discharge; Chest X-ray and ECG on screening and day 14 or on discharge. SARS-CoV-2 (viral load) was looked in on day 5, day 10 and day 14 or at the time of discharge. In case any study patient deteriorates during the study period was managed as per the guideline of that particular hospital and if needed was shifted to ICU. Patients who recovered was discharged as per the national guideline for the COVID-19 hospitalized patients. Patients was contacted at 28 days either over phone or in person to get their health status since discharge. Other information collected included socio-demographic data and details of co-morbidity, concomitant medication, and medical history.

The primary clinical endpoint was duration of hospitalization. The key secondary end point of the trial was the time to clinical improvement after randomization which defined as the time (in days) from randomization of study treatment until a decline of two categories on a six-category ordinal scale of clinical status (1 = discharged; 0 = death) or live discharge from hospital. All other secondary end point of the trial was all causes mortality; duration (days) of supplemental oxygenation; time to 2019-nCoV RT-PCR negativity in nasopharyngeal swab and proportion of patients with serious adverse events that occurred on or after the first dose of Remdesivir for up to 28 days after randomization.

The summary statistics for categorical variables was described with the number and percentage of subjects in each category and for continuous variables with the number of subjects (n), mean, standard deviation (SD). A Pearson chi square test was used to test the differences in proportions, however, the Fisher's exact test was used when a cells have expected frequencies < 5. For continuous data, independent t-test was used to compare and paired t-test was used to determine the mean difference. The primary outcome (duration of hospitalization) was analyzed using independent t-test and the results expressed as mean ± SD with p-value and associated two-sided 95% confidence interval (CI). The lab parameter was (screening vs. day-5) compared using paired t-test with p-value and associated two-sided 95% CI. The primary outcome (duration of hospitalization) and time to required supplemental oxygenation were analyzed through Kaplan-Meier methodology and log-rank test was performed to assess the significance. Cox's proportional hazards model was used to estimates of the treatment effects and was expressed as hazard ratios (HRs) (and associated 95% CI). All statistical tests were two-sided and the level of significance was $p < 0.05$. STATA statistical software, version 15.1 MP, Parallel Edition (StataCorp) was used to perform the analysis.

Results

A total of 60 patients were enrolled in the study after screening and randomized to receive either 5 days' treatment of intravenous Remdesivir along with standard therapy or only standard therapy. Mean age of all the patients was 53.2 ± 12.7 and 83.3% were male (Table 1). More than half of the participants had normal BMI and other 35% had overweight. Among all the patients, 68.3% had comorbidities. Diabetes Mellitus (45%) and Hypertension (40%) were the most common comorbidities. There was no statistically significant difference between two groups in terms of mean temperature, mean blood pressure, mean respiratory rate and mean oxygen saturation at screening. Almost all the patients had fever (98.3%), dry cough (100%), respiratory distress (90%) and loss of taste (88.3). Other symptoms were sore throat (16.7%), headache (41.7%), diarrhea (20.0%), loss of smell (33.3%) and joint pain (23.3%).

	Remdesivir (n = 30)	Control (n = 30)	Total (n = 60)	P-value
Age-Years (Mean ± SD)	54.7 ± 11.7	51.7 ± 13.7	53.2 ± 12.7	0.376
Sex , n (%)				
Male	22 (73.3)	28 (93.3)	50 (83.3)	0.08
Female	8 (26.7)	2 (6.7)	10 (16.7)	
BMI, n (%)				
Underweight,	1 (3.3)	1 (3.3)	2 (3.3)	
Normal weight	14 (46.7)	18 (60.0)	32 (53.3)	0.528
Overweight	11 (36.7)	10 (33.3)	21 (35.0)	
Obesity	4 (13.3)	1 (3.3)	5 (8.3)	
Any Comorbidities, n (%)	25 (83.3)	16 (53.3)	41 (68.3)	0.012
Hypertension	15 (50.0)	9 (30.0)	24 (40.0)	0.114
Diabetes Mellitus	13 (43.3)	14 (46.7)	27 (45.0)	0.795
IHD	4 (13.3))	5 (16.7)	9 (15.0)	1
Temperature (◦ F) (Mean ± SD)	99.1 ± 0.9	99.1 ± 0.9	99.1 ± 0.9	0.824
Systolic BP (Mean ± SD)	125.3 ± 10.4	127.0 ± 7.9	126.2 ± 9.2	0.489
Diastolic BP (Mean ± SD)	77.4 ± 8.4	77.9 ± 8.3	77.6 ± 8.3	0.83
Respiratory rate (breaths/minute)	19.6 ± 1.4	19.4 ± 1.5	19.5 ± 1.4	0.659
O2 saturation (%)	90.1 ± 2.0	90.3 ± 2.0	90.2 ± 2.0	0.793

Table 1: Baseline patient characteristics at screening among two groups (n = 60).

Figure 1: KM analysis to compare proportion discharged from the hospital between treatment and control arms (n = 60).

Covid-19 symptoms	Remdesivir (n = 30)	Control (n = 30)	Total (60)	P-value
Fever (days)	2.2 ± 1.0	2.5 ± 1.2	2.4 ± 1.1	0.28
Dry Cough (days)	7.2 ± 3.0	9.5 ± 3.7	8.3 ± 3.5	0.01
Sore Throat (days)	2.2 ± 2.0	2.6 ± 1.7	2.4 ± 1.8	0.71
Respiratory Distress (days)	4.4 ± 2.4	6.5 ± 3.9	5.5 ± 3.4	0.02
Headache (days)	2.1 ± 1.4	3.6 ± 2.3	2.7 ± 1.4	0.05
Diarrhea (days)	2.0 ± 1.5	2.0 ± 1.3	2.0 ± 1.3	1
Loss of Taste (days)	7.9 ± 2.5	9.2 ± 3.7	8.6 ± 3.2	0.13
Loss of Smell (days)	5.6 ± 2.1	5.4 ± 3.0	5.5 ± 2.5	0.87
Joint Pain (days)	1.6 ± 1.1	2.3 ± 2.4	1.9 ± 1.7	0.47

Table 2: Comparison of duration of covid-19 symptoms between treatment arms.

Total mean duration of hospitalization was 9.3 days. Patients in the Remdesivir group had significantly shorter duration of hospitalization than control group (mean 7.3 ± 2.4, as compared to 10.8 ± 6.1; p-value: 0.013). In Kaplan-Meier (KM) analysis, we found that more than 50% patient were discharged from Remdesivir group on Day 7, almost 75% on day 10 and 100% after day 14. Whereas in control group, 50% patient were discharged on day 9, almost 75% on day 15 and 100% after day 28 (Figure 1).

Dry Cough, Respiratory distress and Headache had resolved significantly (p-value: 0.01, 0.02, 0.05 respectively) earlier in Remdesivir group than the control group (Table 2). There was no statistically significant difference between two groups in all other symptoms including fever, sore throat, diarrhea, loss of taste and smell etc.

We performed a Cox proportional hazard regression comparing Time to Clinical Improvement (TTCI) by day 5, 11 and 14 between treatment groups. There was no statistically significant difference between two groups on Day 5 (HR - 5; 95% CI - 0.58 - 42.80; p-value - 0.142). But, we found statistically significant difference on day 11 (HR - 1.88; 95% CI - 1.03 - 3.36; p-value - 0.038) and day 14 (HR - 2.15; 95% CI - 1.22 - 3.81; p-value - 0.008) between two groups.

In KM analysis, we compared time to require supplemental oxygen between treatment arms and found that there was no difference until day 5. On day 5, half of the patients of control group required oxygen supplementation whereas only one-third patients in Remdesivir group. Among all the patients, only 4 patients had oxygen supplementation from Remdesivir group on day 7, and 12

Treatment Arm	n (%)	Hazard Ratio (HR)	95% CI	P-value
Day-5				
Remdesivir (=30)	5 (16.7)	5	0.58 - 42.80	0.142
Control (n = 30)	1 (3.3)	Reference		
Day-11				
Remdesivir (=30)	27 (90.0)	1.88	1.03 - 3.36	0.038
Control (n = 30)	19 (63.3)	Reference		
Day-14				
Remdesivir (=30)	30 (100.0)	2.15	1.22 - 3.81	0.008
Control (n = 30)	22 (73.3)	Reference		

Table 3: Cox proportional hazard regression comparing Time to Clinical Improvement (TTCI) by day-5, 11 and 14 between treatment arms.

patients from control group (Figure 2). Mean duration of use of supplemental oxygen was 4.2 days in Remdesivir groups and 6.1 days in standard therapy groups which was statistically significant (p-value - 0.029). But, duration of High-flow nasal cannula use was not different among the groups (p-value - 0.128). There were no death or serious adverse events among all the patients. Only 3 patients had non serious adverse events includes nausea. The incidence of adverse events was not found to be significantly different between the Remdesivir group and the control group.

Figure 2: KM analysis to compare Time to requirement of supplemental oxygen between treatment arms.

Discussion and Conclusion

In this open-label, randomized clinical trial among hospitalized patients with Covid-19 due to infection with SARS-CoV-2, we found that treatment with Remdesivir was beneficial for the hospitalized patient. Patients who received Remdesivir had a shorter duration of hospitalization (the primary end point) than those who didn't receive Remdesivir (mean ± SD, 7.3 ± 2.4 days vs. 10.8 ± 6.1 days; p-value - 0.013). Our study findings are consistent with the result of ACTT-1 Study from US where they found patients who received Remdesivir had a shorter time to recovery than those who received placebo (median, 10 days vs. 15 days) [17]. Our study population was treated somewhat earlier in their disease course as we only included the patient whose COVID-19 diagnosis confirmed within 7 days before randomization. Such differences might be expected to favor Remdesivir, providing greater effects in our study population and our results meet this expectation.

In our study we also found that dry cough, respiratory distress and headache had resolved significantly (p-value: 0.01, 0.02, 0.05 respectively) earlier in Remdesivir group than the control group. But, comparison of duration of covid-19 symptoms between two treatment arms found no difference in case of other symptoms like fever, sore throat, loss of taste, loss of smell, diarrhea etc. We also found that treatment with Remdesivir might have shown better time to clinical improvement at the end of the treatment. Although we didn't find any significant differences between the two groups on Day 5. But, we found statistically significant difference on day 11 (HR - 1.88; 95% CI - 1.03 - 3.36; p-value - 0.038) and day 14 (HR - 2.15; 95% CI - 1.22 - 3.81; p-value - 0.008) between two groups.

Our data also suggest that treatment with Remdesivir may have prevented the progression to more severe respiratory disease as it was significantly reduced the time to requirement of supplemental oxygen between treatment arms. Treatment with Remdesivir was associated with fewer days of subsequent oxygen use for patients receiving oxygen at enrollment. Cumulatively, these findings suggest that treatment with Remdesivir may not only reduce the disease burden but may also decrease the use of scarce health care resources during this pandemic.

The findings in our trial should be compared with those observed in other randomized trials of Remdesivir. A study in China early in the pandemic showed a shorter time to improvement (a two-point improvement) with Remdesivir: 21.0 days in the Remdesivir group and 23.0 days in the placebo group (HR for clinical improvement, 1.23; 95% CI, 0.87 to 1.75) [21]. That trial did not complete full enrollment owing to local control of the outbreak and restrictions on hospital bed availability resulted in most patients being enrolled later in the course of disease. In another open-la-

bel, randomized study of Remdesivir in hospitalized patients with moderate-severity Covid-19, patients who received Remdesivir for 5 days had higher odds of clinical improvement than those receiving standard care (odds ratio, 1.65; 95% CI, 1.09 to 2.48; P = 0.02) [22]. So it is evident that the findings of this study support our findings regarding the efficacy of Remdesivir.

Although the study sample was too small (n = 60) to draw any solid conclusions, the results provide evidence of the potential benefit of early intervention with the Remdesivir for the treatment of adult hospitalized patients diagnosed with COVID-19. Also the interpretation of these results is limited by the lack of a randomized placebo control group and the open-label design. We designed this as an open-label trial only to avoid psychological dilemma of the patients of using placebo. The concept and acceptance of placebo controlled trial is very limited in our country. On the other hand, given the stretched health care resources during the pandemic, it seemed appropriate to allow the patients to be discharged from the hospital as soon as medically indicated, regardless of whether they had completed the full assigned course of treatment with Remdesivir or placebo. Another important limitation is that we did not have SARS-CoV-2 viral-load results during and after treatment, owing to the variability in local access to testing and practices in Bangladesh.

Our study findings suggest that intravenous Remdesivir has beneficial effects on patients who are hospitalized with Covid-19 and require supplemental oxygen therapy. Primarily it reduced the duration of hospitalization and proportion of time to clinical improvement among the hospitalized patients with Covid-19. It also shortened the period of use of oxygen supplementation without any additional safety concern. A larger randomized placebo controlled clinical trial of Remdesivir treatment appears to be warranted to validate these important findings.

Conflict of Interests

This is to certify that the Investigators do not have any matters which might give rise to a real or perceived conflict of interest. There is no existence of any personal interest, pressure of biasness and involvement with any organization which can mislead during the study procedure. The study was supported and study drug (Bemsivir®) was provided by the unconditional unrestricted research grant from Beximco Pharmaceuticals Ltd.

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